DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

M02351

CBER - 99- 008

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

December 11, 1998

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Hans Dieringer, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
Dade Behring AG
Bonnstrasse 9
CH-3186 Dudingen
Switzerland

Dear Dr. Dieringer:

An inspection of Dade Behring AG, Bonnstrasse 9, CH-3186 Dudingen, Switzerland, was conducted from October 12, 1998 through October 16, 1998. During the inspection, violations of Section 501(h) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations, Subchapter F, Parts 600-680, and Subchapter H, Part 820 were documented as follows:

1. Failure to establish, maintain, and follow procedures to adequately control environmental conditions that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(c) and 660.20(a)] in that:

   a. there is no personnel monitoring of operators in filling room – during dynamic conditions.

   b. Standard Operating Procedure (SOP) MFG0758, entitled "Sterile Assurance Level", does not address planned interventions during media fills, investigation and identification of microbial isolates when a — % contamination rate is achieved, and personnel monitoring during dynamic conditions in filling room —

   c. there is no written procedure that addresses frequency of environmental monitoring sampling and investigation and identification of microbial isolates for the filling, filtration, and cell culture rooms.

d. there are no written procedures that require the documentation of sterilization runs for filters such as the records of cycle temperatures, times, pressures, and the results of biological indicator testing used during each sterilization run.

2. Failure to establish, maintain, and follow procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(e) and 660.20(a)] in that:

a. the ambient temperature ————————) water system which is used for the production of Reagent Red Blood Cells (RRBC) and Blood Grouping Reagents (BGR) has not been validated.

b. the following were observed in regard to the — water system and recirculating loop:

1. the t ——— storage tanks and the elements in the water distribution loop have never been cleaned, sanitized, or drained.

2. the vented —— storage tank does not have a vent filter.

3. numerous instances were observed of point-of-use (POU) hoses on the bottom of sinks and POU hoses which contained water.

4. the drain lines of the pre-filters and the — concentrate lines were on the floor.

5. alarms for pressure drop and conductivity on the — membranes and pre-filters have not been qualified for use.

6. there is no established criteria for changing the — pre-filters and the pre-filters are not integrity tested.

c SOP MFG0228, entitled "Water Monitoring":

1. does not provide specifications for — water microbial quality or Total Organic Carbons,

2. does not assure that water samples are representative of water used in production in that the SOP requires a flush of the lines prior to sampling, however, the manufacturing and laboratory procedures do not require a ——— flush prior to use,

3. the method for analysis of — Water by ——— filtration described in the SOP has not been validated to assure microbial recovery. Furthermore, the SOP does not include the amount of water to be analyzed, the incubation time, temperature, and type of culture media to be used

d. microbial sanitizer efficacy studies for the use of —— n the manufacturing area and ——— in the cell culture area did not include a challenge of the cleaning agents to known amounts of bacterial suspensions.

3. Failure to establish, maintain, and follow procedures for implementing corrective and preventative action including requirements for investigating the cause of nonconforming product and identifying the action(s) needed to correct and prevent recurrence of nonconformities and other quality problems [21 CFR 820.100] in that:

a. SOP MFG0220, entitled "Stability Procedure for Immunohematologic Products", does not describe the action to be taken when stability tests are found to be out-of-specification for Reagent Red Blood Cell products (US) and does not describe retesting procedures.

b. Reagent Red Blood Cell (RRBC) nonconforming reports # 98086, # 98099, # 97048, # 97067, # 97076, # 97084, do not include investigations to identify the cause for out-of-specification hemolysis results. Also, RRBC nonconforming report # 98040 did not include an investigation to identify the contaminate for a failed bulk sterility test.

4. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications [21 CFR 820.70(a)] in that:

a. there are no data to support the ——— expiration date for autoclaved vials and the expiration dated for autoclaved stoppers.

b. preservative effectiveness studies have not been performed for Blood Grouping Reagents and Reagent Red Blood Cells

c. there are no cleaning validation studies for the filling machine for Blood Grouping Reagents and Reagent Red Blood Cells.

5. Failure to establish, maintain, and follow procedures for process validation in order to ensure that processes have been adequately validated and that the specified requirements continue to be met [21 CFR 820.75] in that;

a. container/closure integrity validation has not been performed for Blood Grouping Reagents and Reagent Red Blood Cells.

b. validation studies have not been performed for the primary filters and pre-filters used for in-line sterilization of Reagent Red Blood Cells buffer solution and Blood Grouping Reagent bulk solution.

c. the —— autoclave has not been validated for sterilization of in-line filters. Studies have not been conducted to assure that autoclave cycles do not affect the physical integrity or bacterial barrier/retention ability of filters.

d. the validation campaign for the ——— autoclave used for the preparation of sterility test media did not include temperature mapping and heat penetration studies.

e. The 1997 validation study of the —— Autoclave used to sterilize vials and stoppers does not include a temperature mapping study, an empty chamber mapping study, the identification of slowest to heat objects and slowest to heat areas of the autoclave, the identification of size and composition of mixed loads of stoppers and other components, determination of half-cycle time, and the examination of the physical integrity of the vial stoppers following autoclave cycles.

6. Failure to establish and maintain acceptance procedures for incoming product which shall include the inspection, testing, or verification of incoming product to show conformance to specified requirements [21 CFR 820.80(b)] in that there is no verification of the Certificate of Analysis of the purchased media used for environmental monitoring, sterility, and water testing.

7. Failure to evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements, and to document the evaluation [21 CFR 820.50(a)]. There are no records to show that the contract laboratory, ———, the culture media supplier, ———, and the filter supplier, ——— have been subjected to formal qualification or audit.

8. Failure to ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use [21 CFR 820.70(g)] in that

a. the — filter on the ——— autoclave has not been changed and there are no criteria or written procedures for filter changing.

b. there are no written procedures for regular cleaning and sanitization of the autoclave.

c. temperature mapping and distribution studies were not conducted for the sterility test incubators in room

9. Failure to ensure that all inspection, measuring, and test equipment is suitable for its intended purposes and is capable of producing valid results [21 CFR 820.72] in that there are no written procedures for the calibration of the Getinge autoclave and the thermocouples, temperature set points, and pressure gauges have not been calibrated on the ——— autoclave.

Your written response of November 2, 1998, to the Form FDA-483 issued at the close of the inspection is currently under review. You will receive our assessment of your responses upon completion of our review. Corrective actions addressed in your previous letter may be referenced in your response to this letter, as appropriate.

Neither the above violations nor the observations noted on the Form FDA 483 presented to your firm at the conclusion of the inspection are intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to ensure adherence to each requirement of the Federal Food, Drug, and Cosmetic Act and the applicable regulations and standards. The specific violations noted in this letter and the Form FDA 483 may be symptomatic of serious underlying problems in your establishment's manufacturing and quality systems. You are responsible for investigating and determining the causes of the violations identified by FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action without further notice. Such action includes license suspension, and/or revocation; seizure; civil penalties and/or import alert, which would prevent your product from entering the U.S. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. In addition, no license applications or supplements for devices to which the deficiencies are reasonably related will be approved until the violations have been corrected.

You should respond to FDA in writing within 15 working days of receipt of this letter of the specific steps you have taken to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. FDA will verify your implementation of promised corrective action during the next inspection of your facility. Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Annette Ragosta at (301) 827-6322.

Sincerely,

Daniel L. Michels
Acting Director
Office of Regional Operations